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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/477,147	06/07/95	LIVINGSTON	P 43016-D/JPW/

HM21/1221

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EXAMINER	
DUFFY, P	
ART UNIT	**PAPER NUMBER**
1645	15

DATE MAILED: 12/21/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	08/477,147	Livingston et al
	Examiner	Group Art Unit
	Duffy	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 10-1-98 .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 57-77 is/are pending in the application.

Of the above claim(s) 57-70 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 71-77 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claim(s) 57-70 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

Response to Amendment

1. The amendment filed October 1, 1998 has been entered into the record. Claims 57-77 are now pending.

2. Newly submitted composition claims 57-70 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the compositions as claimed are distinct because they can be used in a materially different process such as linked to a column for purification of cross reactive antibodies, in an *in vitro* method to study immune responses or in an *in vitro* method to generate monoclonal antibodies.

Since applicant has received an action on the merits for ***the originally presented methods*** invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 57-70 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. This application contains claims 57-70 drawn to an invention nonelected by original presentation. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Maintained

Double Patenting

5. Claims 71-77 are *provisionally* rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 65-71 of copending

Application No. 08/477,097. Although the conflicting claims are not identical, they are not patentably distinct from each other because they all claim conjugating proteins to gangliosides through the ceramide portion and thus the particular method species drawn to GM2 or GM3 claimed in the copending application would anticipate the instant genus method claims.

6. Claims 71-77 are *provisionally* rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 66-72 of copending Application No. 08/475,784. Although the conflicting claims are not identical, they are not patentably distinct from each other because they all claim conjugating proteins to gangliosides through the ceramide portion and thus the particular method species claimed in the copending application would anticipate the instant genus method claims.

7. Claims 71-77 are *provisionally* rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 71-77 of copending Application No. 08/196,154. Although the conflicting claims are not identical, they are not patentably distinct from each other because they all claim conjugating proteins to gangliosides through the ceramide portion and thus the particular method species claimed in the copending application would anticipate the instant genus method claims.

8. Claims 71-77 are rejected under 34 U.S.C. 112, first paragraph is maintained for reasons made of record for claims 44 and 46-56 in Paper No. 13, mailed 4-1-98.

Applicants' have asserted that the claims are no longer drawn to vaccines and thus the issues with regard to effective treatment or prevention of cancer of record in the last office action is moot. This is not persuasive because the claims 72-77 are clearly drawn to treatment and prevention of cancer by administration of an agent which the specification teaches generates an antibody response. Applicants have not provided any evidence the administration of the

composition whether or not entitled vaccine has any effect for treatment. Applicants have not provided any evidence to show that the administered agents prevent cancer in any disease state. The claims remain not enabled for reasons already made of record. The compositions are taught in the specification to act through enhancement of the immune response and are thus still considered "vaccines" inasmuch as, vaccines encompass any prophylactic or therapeutic material containing antigens on administration to man will stimulate active immunity (see The Dictionary of Immunology attached) and it is this active immunity which applicants propose throughout the specification which is allegedly capable of treating or preventing cancer. Thus, claims drawn to treatment and prevention of cancer are not enabled for reasons already made of record.

Applicants' arguments regarding the issue of "derivative" have been carefully considered but are not persuasive for the reasons set forth below. Applicants' argue that derivatives have been taught and point to page 12, lines 4-13. This passage is not persuasive because the derivatives are in fact conjugates with other proteins and is thus not commensurate in scope with the claims. The term derivative clearly encompasses changes to the primary structure of Keyhole Limpet Hemocyanin (KLH). Derivative is not defined in the specification or the claims to exclude amino acid changes and modifications of the primary amino acid structure of KLH. The derivatives disclosed by applicants are in fact conjugates with other proteins and thus applicants arguments are not commensurate in scope. Applicants' provide no guidance as to which changes in KLH residues or derivations of amino acids would function appropriately and thus the skilled artisan would have to resort to unguided experimentation. Absent a guidance for modification of the sequence per se, any experimentation would be undue. The specification fails to provide even the most rudimentary guidance for a starting point for chemical derivation of

the KLH sequence other than conjugation with other proteins. Thus, applicants arguments are not commensurate in scope with the scope of "derivative". The rejection is maintained for reasons made of record.

New Rejections Based on Amendment

9. Claims 72-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are rendered indefinite because they depend from claims withdrawn from consideration as drawn to an invention non-elected by original presentation. Correction is required.

10. Claims 71-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims now recite the phrase ".. comprising a ganglioside conjugated through the ceramide portion of the ganglioside to a Keyhole Limpet Hemocyanin..". This phrase and the concept of this type of conjugation is not supported by the written description of the specification as originally filed. The passages to which applicants' point for support, fail to convey conjugation of the ganglioside through the ceramide portion. These passages do not even mention the ceramide portion. This issue is best resolved by applicants pointing to the specification by page and line number where support for the now claimed limitation is found.

11. Claims 71-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al (Cancer Research, 49:7045-7050, 1989) in view of Irie et al (U.S. Patent No. 4,557,931, published December 10, 1985) and Ritter et al (Cancer Biology, 2:401-409, 1991).

Livingston et al (Cancer Research, 49:7045-7050, 1989) teach a composition administered to melanoma patients for stimulating the production of antibodies directed to a carbohydrate epitope on the ganglioside, GM2 (p7046-7048). Livingston et a teach that the GM2 is administered in conjunction with an adjuvant, Bacillus Calmette-Geurin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline (p 7048, column 1, paragraph 3 and paragraph bridging p 7046-47). Livingston et al teach that the melanoma recurrence was delayed in patients developing GM2 antibodies after vaccination (p 7048 paragraph 1, and column 2, paragraph 2). Livingston et al teach that more patents produced IgM antibodies that IgG antibodies to the GM2 (p 7047 paragraph bridging columns 1-2). Livingston et al also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (p 7045, column 1, paragraph 2). Livingston et al do not teach the conjugation of the GM2 vaccine with Keyhole Limpet Hemocyanin (KLH) through the ceramide portion of the ganglioside or use of any of the other gangliosides in a method to induce an immune response or cancer treatment.

Irie et al teach conjugation of ganglioside GM2 to a non-toxic protein carrier, such as albumin, using ozonolysis (column 5, see B., lines 19-68) which conjugates a the GM2 through the ceramide portion. Irie et al teach that the fatty acid of ceramide maybe removed leaving sphingosine and thus the coupling takes place through the amine group of the sphingosine moiety (column 2, lines 64-69). Irie et al teach that the conjugated GM2 can be used as a

vaccine to stimulate an immune response and raise the anti-GM2 titer in mammals (column 2). Irie et al differ by not conjugating the GM2 to KLH.

Ritter et al (Cancer Biology, 2:401-409, 1991) teach that the IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (p 406, paragraph 1). Ritter et al discloses the advantage of using an IgG antibody response (versus IgM) against gangliosides is that IgG a) has a higher affinity; b) is better able to penetrate solid tissues; c) is able to mediated antibody-dependent cell-mediated cytotoxicity; and d) is generally detectable in the serum for longer periods after immunization.

It would have been *prima facie* obvious to one of ordinary skill in the art to modify the GM2-albumin ceramide conjugate of Irie et al by substituting KLH for albumin and to substitute the resulting GM2-KLH ceramide conjugate for the GM2 in the immunization composition of Livingston et al for active immunization for generating antibody response for melanoma treatment because Irie et al teach that the GM2 conjugated through the ceramide (sphingosine) portion can be used as a vaccine to simulate an immune response and raise the anti-GM2 titer in mammals and Ritter et al teach that the IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (p 406, paragraph 1) and Ritter et al discloses the advantages of generating and IgG as opposed to an IgM antibody response and optimization of the dosage, route of administration and number of sites to administer the composition as combined above is well within the skill of the art.

12. Applicants' arguments are moot in view of the new grounds of rejection set forth above in view of the amendments to the claims to recite that the ganglioside is linked to KLH through the ceramide portion which applicants now recite as the novel aspect of the invention.

Status of Claims

13. All claims stand rejected.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The

examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
December 19, 1998

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600